REMARKS

The Invention

In general, the invention as presently claimed features a mouse having two transgenes. The first transgene, which includes a regulatory gene encoding a regulatory protein, is integrated into an endogenous gene such that two events occur. First, the endogenous gene is mutated by the insertion of the transgene. Second, expression of the regulatory gene is regulated by the promoter of the endogenous gene.

The second transgene includes a gene operably linked to a regulatory sequence that is under the control of the regulatory protein encoded by the first transgene; this gene is referred to hereinafter as "the regulated gene." Gene regulation may be positive (i.e., the expression of the regulated gene may be increased in the presence of the regulatory protein) or negative (i.e., the expression of the regulated gene may be decreased in the presence of the regulatory protein). In either case, because the expression pattern of the regulatory protein is determined by expression of the endogenous gene, the end result is that it is the endogenous gene's expression that determines how the regulated gene is expressed.

Rejections under 35 U.S.C. § 103(a)

The sole rejection is of all pending claims (claims 1, 2, 6-13, 18, and 20-24) for obviousness in view of Furth et al. (Proc. Natl. Acad. Sci. USA 91:9302, 1994) in combination with one or more of Friedrich et al. (Genes Devel. 5:1513, 1991), Zhang et al. (Biochem. Biophys. Res. Comm. 227:707, 1996), Bremer (Nucleic Acids Res.

20:5484, 1992), Smith (U.S. Patent No. 6,150,169), and Borrelli (Proc. Natl. Acad. Sci. 85:7572, 1988). Applicant respectfully traverses this rejection.

Claims 1, 2, 6-8, 20, 21, 23, and 24

Claims 1, 2, 6-8, 20, 21, 23, and 24 are rejected as being obvious over two references--Furth and Friedrich. According to the Office:

> It would have been obvious to one of ordinary skill of art to make a transgenic mouse comprising the binary temporal control system as taught by Furth et al. and modifies [sic] the transgenic mouse by inserting the regulatory protein into an endogenous gene and utilize the endogenous protein taught by Friedrich et al. The ordinary skilled artisan would have been motivated to do so not only to study the function of the mutated gene (as taught by Friedrich), but also provides a gene regulatory system that utilizes the advantage of tissue specific expression of an endogenous gene.

The prior art provides no motivation to combine the teachings of Furth with those of Friedrich

In order to establish a *prima facie* case of obviousness, the Office has the burden to show that one would have been motivated to combine the references to arrive at the claimed invention. In the present case, the cited art provides no such motivation.

Furth, the primary reference, uses mice that contain two transgenes. The first transgene includes the TetR/VP16 transactivator gene under the control of the human cytomegalovirus early gene 1 promoter-enhancer (hCMV *IE1*). The second transgene contains a reporter gene (either the luciferase gene or a nuclear β-galactosidase gene) under the control of a basal CMV promoter fused to seven copies of the tetO sequences. In these mice, expression of the reporter gene is initially prevented by the administration

of tetracycline. When tetracycline is withdrawn, the reporter gene is expressed. The teachings of Furth, in fact, are quite similar to those of St. Onge et al. (Nucl. Acid Res. 24: 3875, 1996), which, in the Office action dated March 22, 2004, was combined with Friedrich to form the basis of an earlier obviousness rejection, which was later withdrawn. The Furth reference suffers from the same deficiencies as the St. Onge reference, which is not surprising as St. Onge is the second author on the Furth paper and vice versa.

Friedrich, the second reference relied upon by the Office, discloses the use of a promoter trap, in which "expression of a reporter gene can initiate only from an endogenous promoter because the reporter gene lacks its own promoter." As is clear from this and other passages of Friedrich, the authors' intent was to develop a more rapid screen for mutagenized animals. For example, Friedrich summarizes the prior methods as being "laborious and time consuming," and states that "a method that would allow screening and selection for mutations in vitro would be useful." To this end, Friedrich developed a screen that "involves the introduction of a reporter gene preceded by a splice acceptor into ES cells." Friedrich further characterizes the ideal reporter gene as being one that "should be innocuous, allow selection for mutagenic insertions, and include a means to easily monitor the tagged promoter once the ES cell clone has been used to create chimeras and transgenic lines."

In looking at these references, then, Friedrich is solely focused on a singular problem, namely the development of a method for more easily selecting insertion

mutations in mice. Friedrich teaches only the use of reporter genes, and is silent on the use of a regulatory gene, as is required in claim 1.

In addition, there are at least two important distinctions between the mice of Furth and the claimed mouse. First, both of Furth's transgenes are intended to be ubiquitously expressed. Indeed, it is for this reason that at least one of the promoters was chosen ("the hCMV *IE1*promoter/enhancer was chosen because it is expressed in a broad spectrum of tissues in transgenic mice"). In contrast, in the mouse of the present invention, the first transgene may be expressed in a spatially restricted manner, depending on the expression pattern of the gene into which the transgene inserts. Moreover, Furth's transgene does not necessarily mutagenize an endogenous gene, while mutagenization of an endogenous gene is a requirement in the claimed mouse. The Office nonetheless contends that one skilled in the art would have been motivated to combine the teachings of Friedrich and Furth "to utilize the advantage of tissue specific expression of an endogenous gene" in a transgenic mouse. The Office has provided no support for this conclusion. As the Federal Circuit recently observed:

> Most if not all inventions arise from a combination of old elements. . . . Thus, every element of a claimed invention may often be found in the prior art. . . . However, identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention. . . . Rather, to establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant.

In re Kotzab, 217 F.3d 1365, 1369-70, 55 USPQ2d 1313, 1316 (Fed. Cir. 2000) (citations omitted). The Office can satisfy the burden of showing obviousness of the combination

"only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references." *In re Fritch*, 972 F.2d 1260, 1265, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992).

This standard has not been met in the present case, nor could it be as motivation does not exist for the combination of these references. Friedrich was solely focused on the use of reporter genes in promoter trap-mediated mutagenesis as a means by which the efficiency of their method could be improved, and does not consider the use of any other gene or combination with a second transgene construct. Furth uses a ubiquitously expressed regulatory protein encoded by a non-mutagenizing transgene to control reporter gene expression and is entirely silent on the idea of using promoter trap constructs. Neither reference therefore provides any objective teaching that would lead an individual to combine them in a manner so as to result in the claimed invention. Indeed, combining the references as proposed by the Office would further the goal of neither Furth nor Friedrich.

In view of the foregoing, on this basis alone, Applicant respectfully requests that the rejection of claims 1, 2, 6-8, 20, 21, 23, and 24 as being obvious over Furth in view of Friedrich be withdrawn.

No combination of the cited references results in the claimed invention

In order to establish a *prima facie* case of obviousness, in addition to showing that one would have been motivated to combine the references in a manner that would result

in the claimed invention, the Office has the burden of showing that a combination of the references teaches or suggests every claim limitation.

Here, even if one would have been motivated to combine the teachings of Furth with those of Friedrich, one would not have arrived at the claimed invention. Instead, the resulting mouse would have three transgenes (the two taught by Furth and the one taught by Friedrich) and would in no way resemble the presently claimed mouse. To even approximate the claimed mouse, one would have needed to select particular components of Furth's transgenes to combine with particular components of Friedrich's transgene, and them arrange them in a specific order, and all of this being done without the slightest suggestion in either reference to do so.

Moreover, the first transgene of the claimed mouse requires a regulatory gene encoding a regulatory protein and a transcription terminator. This transgene is integrated into an endogenous gene of the mouse such that (i) the regulatory gene is positioned for expression under control of the endogenous gene's promoter, and (ii) the endogenous gene is mutated. The second transgene includes a gene operably linked to a regulatory sequence regulated by the regulatory protein.

The Office fails to indicate which reference teaches or suggests the claimed transcription terminator. Applicant has reviewed the cited references and submits that no combination could teach the claimed mice because each reference fails to disclose such a transcription terminator. Furth, the primary reference, discloses a transgene including a regulatory gene, but this transgene does not have a transcription terminator. Friedrich, the second reference relied upon by the Office, similarly fails to mention transcription

termination sequences or their desirability, thereby also failing to suggest or provide any motivation for inserting these sequences into a mouse. Neither of these references teaches termination site sequences or mentions the use of such sequences in the generation of transgenic mice.

In contrast, each of the pending claims recites a mouse having a transgene that contains a transcription termination site sequence. As described in the specification, for example, at page 17, such termination sequences provide special advantages. Notably, the use of these sequences prevents read-through transcription of flanking cellular sequences when the terminator is integrated into a host chromosome. In addition, the use of such transcription termination sites provides significantly increased mutagenic capability by blocking potential bypassing of insertions through alternative splicing events that make use of fortuitous, downstream chromosomal splice sites.

As no combination of the cited references results in the claimed invention, on this basis as well, the rejection of claims 1, 2, 6-8, 20, 21, 23, and 24 as being obvious over Furth in view of Friedrich should be withdrawn.

Claims 9-13

Claims 9-13 are rejected as being obvious over Furth in view of Friedrich and in further view of Zhang (claims 9-12), Bremer (claim 13), Smith (claim 18), and Borrelli (claim 22). Furth and Friedrich are discussed above. Zhang discloses the use of green fluorescent protein as a reporter protein. Bremer simply discloses the VDE restriction site and VDE-mediated digestion. Smith teaches the use of an IRES to facilitate the

expression of a heterologous gene in a host genome. And Borrelli discloses a toxic herpes simplex viral vector for use in studying cell lineage. None of these references remedies the deficiencies of Furth or Friedrich by providing either the transcription terminator or the motivation to make the claimed mouse. Reconsideration and withdrawal is respectfully requested.

CONCLUSION

Applicant submits that the claims are now in condition for allowance, and such action is respectfully requested. If the Office deems that there are remaining issues, Applicant respectfully requests a telephonic interview between the Office and the undersigned.

If there are any charges, or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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